Bromine, bear-claw scratch fasciotomies, and the Eagle effect: management of group A streptococcal necrotising fasciitis and its association with trauma

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Necrotising fasciitis is a rare, but potentially fatal, soft-tissue infection. Historical depictions of the disease have been described since classical times and were mainly recorded in wartime reports of battle injuries. Although several different species of bacteria can cause necrotising fasciitis, perhaps the most widely known is group A streptococcus (GAS). Infection control, early surgical debridement, and antibiotic therapy are now the central tenets of the clinical management of necrotising fasciitis; these treatment approaches all originate from those used in wars in the past 150 years. We review reports from the 19th century, early 20th century, and mid-20th century onwards to show how the management of necrotising fasciitis has progressed in parallel with prevailing scientific thought and medical practice. Historically, necrotising fasciitis has often, but not exclusively, been associated with penetrating trauma. However, along with a worldwide increase in invasive GAS disease, recent reports have cited cases of necrotising fasciitis following non-combat-related injuries or in the absence of antecedent events. We also investigate the specific association between GAS necrotising fasciitis and trauma. In the 21st century, molecular biology has improved our understanding of GAS pathogenesis, but has not yet affected attributable mortality.

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Introduction

Phagedena, hospital gangrene, haemolytic streptococcal gangrene, and flesh-eating disease are various terms used to describe necrotising fasciitis.[1] Although the cause is often polymicrobial, necrotising fasciitis is most associated with the Gram-positive bacterium *Streptococcus pyogenes*, also known as group A streptococcus (GAS), in part because it was implicated in the first large case series of necrotising fasciitis described.[2] The original term necrotising fasciitis was suggested by Wilson in 1952,[3] and is based on the pathological changes: a rapidly progressing infection that consistently resulted in fascial necrosis. Despite its varied nomenclature, this potentially life-threatening soft-tissue infection is easily recognised in historical reports.

Hippocrates described the association between a necrotising soft-tissue infection and injury in the 5th century BCE: "Many were attacked by the erysipelas…when the exciting cause was a trivial accident or a very small wound…the erysipelas would quickly spread wisely in all directions… Flesh, sinews, and bones fell away in large quantities…"[4] Subsequently, there are many disorders consistent with necrotising fasciitis in medical literature (figure 1), with particular reference to traumatic wounds acquired during wartime.[6–8] The American Civil War in the late 19th century changed the epidemiology and management of necrotising fasciitis (figure 1), with detailed descriptions of hospital gangrene[9] and a trial of bromine antisepsis for this disease.[10] Around the same time, the specialty of microbiology was developing and in 1874, the name Streptococcus was proposed for the organisms isolated from wound infections.[11] The two World Wars and the intervening period improved our understanding of streptococci and necrotising fasciitis, and emphasised the importance of surgery.[2,12,13] World War 2 stimulated large-scale antibiotic production, which was a major transition in the management of combat-related wounds.[14,15]

At the end of the 20th century, the incidence of necrotising fasciitis increased in some countries, such as New Zealand.[16] In particular, reports increased of severe necrotising fasciitis caused by GAS worldwide in countries such as the UK, Norway, Canada, and the USA.[17–21] Although GAS necrotising fasciitis is rare (UK incidence is 1·7 per 1 000 000 people per year),[22] recent case fatality rates are 13–31%,[23–26] and rise to more than 40% when associated with streptococcal toxic shock syndrome (STSS).[22] This morbidity prompted the introduction of antibiotics targeted at toxin production and the use of adjunctive intravenous immunoglobulin. Notable in the modern literature are reports of necrotising fasciitis following non-penetrating, minor injury such as muscle contusion[27–34] by contrast with historical reports, which were ostensibly linked to penetrating injury typified by combat wounds.[4,9,12,35,36]

In this Historical Review, we focus on GAS necrotising fasciitis and use historical data to review how management of the disorder developed during three distinct periods (the late 19th century, the early 20th century, and after World War 2), leading to the multifaceted approach used nowadays. We also examine the association between blunt or penetrating trauma and GAS necrotising fasciitis. Although reporting bias during wartime could partly account for the association between trauma and necrotising fasciitis, evidence from peacetime also supports this association. Because the term necrotising fasciitis was only conceived in 1952, we focus on disorders that have descriptive similarities with necrotising fasciitis in the medical literature. In the 21st century, modern scientific techniques to understand underlying pathophysiology will hopefully further refine management of this devastating disease process.

Figure 1: **19th century illustrations of hospital gangrene**
(A) Hospital gangrene affecting the hand following a lancet puncture of an abscess. Watercolour by William Alfred Delamotte, 1847. (B) Hospital gangrene of an arm stump. Reproduced with permission from plate XV in *The Medical and Surgical History of the War of the Rebellion, 1861–65*.[5] Images are courtesy of Wellcome images, the Wellcome Trust.

Infectious diseases pre-19th century: miasmas and laudable pus

Hippocrates (fifth century BCE) and Galen (second century CE) greatly influenced medical practice in Europe up to the 19th century, before which infectious diseases were assumed to originate from miasmas–poisonous vapours emanating from decomposing organic matter. Furthermore, Hippocrates believed that disease susceptibility was related to an imbalance of four bodily fluids or humours. Galen proposed that pus expelled from wounds rebalanced the humours (*pus bonum et laudabile*) and was beneficial to patients.[37] Unfortunately, Galen's theory was interpreted as pus being necessary for wound healing, and pus formation was actively encouraged. Thick, creamy laudable pus (most probably staphylococcus infection) was encouraged and distinguished from thin, watery pus (most probably streptococcus or Gram-negative infection), which was associated with mortality. The erroneous concept of laudable pus was not refuted until the second half of the 19th century with the introduction of antisepsis by Joseph Lister.[38]

The late 19th century: hospital gangrene, infection control, and bromine during the American Civil War

An estimated 700 000 soldiers died during the American Civil War from 1861 to 1865,[9] the bloodiest war in US history.[5] However, only a third of deaths were directly related to battlefield trauma, the remainder were caused by infectious diseases such as typhoid, dysentery, and yellow fever.[39] Of the 253 142 wounds reported in the permanent registers of the US Surgeon General's office, 59 376 (23%) were flesh wounds, which included hospital gangrene.[5] Although hospital gangrene has been attributed to *S pyogenes*, other organisms cannot be ruled out without historical specimens.

Joseph Jones, a Confederate Army surgeon, described vividly the rapid progression of hospital gangrene[9] and the effect on the underlying tissues: "...a purple or blue spot is first perceived...I have seen the skin in the affected spot melt away in twenty-four hours into a greyish and greenish slough, whilst a deep blue and purple, almost black areola, surrounding the dead mass, spread rapidly in ever increasing circles...Hospital gangrene destroys the cellular and adipose tissues most rapidly; the muscles, nerves, large blood-vessels, and the bones resist its action for a greater length of time."[9] Although French and British naval surgeons recognised hospital gangrene before the American Civil War,[1] Jones' depiction has been credited as the first modern description of necrotising fasciitis.[40] Although skin discolouration is a late feature of GAS necrotising fasciitis, this description is also compatible with cutaneous anthrax and clostridial necrosis and thus, whether Jones is describing GAS necrotising fasciitis remains inconclusive.

Jones believed in miasma theory and attributed the spread of hospital gangrene to "crowding together of sick and wounded soldiers in imperfectly ventilated and filthy hospitals...",[9] which he felt led to favourable conditions for the "...development of hospital gangrene upon reception of wounds".[9] Jones recommended infection control measures to tackle hospital gangrene and noted that "the wounded should never be placed in wards with patients suffering from anyone of the contagious or infectious diseases...erysipelas, pyaemia, or hospital gangrene; and these various diseases should not be indiscriminately mixed together".[9]

Middleton Goldsmith was a Union surgeon in Louisville, Kentucky during the American Civil War. He was struck by the high mortality associated with hospital gangrene and rapid spread on wards, and believed the disorder happened spontaneously "where the wounded are crowded together—where the wards are filled with the stench of traumatic profluvia, and receive the air of sewers and cellars".[10] He postulated that epidemics were linked, and that their control should reduce mortality. Goldsmith reviewed various treatments including corrosive acids and caustic alkalis, which prevented tissue spread of gangrene, but destroyed remaining viable tissue and were only applicable to open wounds.[10] He became interested in halogens like chlorine, fluorine, and bromine after noticing patients recovered better on wards in which bromine deodorants were being used as disinfectants.[39]

Goldsmith recommended surgical debridement for hospital gangrene followed by bromine injections into muscle layers and exposed surfaces. He monitored disease progression through the wound's odour. He did a trial of bromine therapy in 334 patients with hospital gangrene, 304 of whom received bromine either alone or after other treatments (figure 2). Eight patients who received bromine died (2·7% mortality) compared with eight of 13 given nitric acid (61·5% mortality) and five of 13 given other remedies (38·5% mortality).[10] Treatments that were used before bromine was trialled by Goldsmith, which included lead salts, caustic potash, or nitric or carbolic acid, yielded mortality rates of around 25%,[36,41] and cumulative mortality from hospital gangrene was 45·6%.[5] His work acknowledged the importance of infection control through antisepsis in wound infection management.

Germ theory and the rise of streptococcus

In the late 19th century, when America was being reconstructed after the Civil War, microbiology research was developing in Europe. During this time, streptococcus was recognised as a cause of disease. The scientific community was attempting to identify the cause of suppurative infections. Research often included inoculating samples from affected individuals (animals or human beings) into other animals to observe disease progression. One proponent was Robert Koch. In 1876, when investigating the cause of traumatic infective diseases, Koch isolated anthrax bacillus, thus proving the germ theory of disease and beginning the golden age of bacteriology.[42,43]

In 1868, German surgeon Theodor Billroth isolated chain-forming bacteria from wound pus and named them Streptococcus (from the Greek *strepto* for chain, and *kokkus* for berry).[11] Louis Pasteur isolated a chain-forming coccus from the blood and uterus of a woman with puerperal fever 11 years later in France, attributing the disease to microorganisms invading the wounded uterine surface after childbirth.[44] In 1882, another German surgeon, Friedrich Fehleisen, cultured streptococci from the skin of patients with erysipelas and reproduced signs of erysipelas following inoculation into human beings, thus supporting the association between streptococcus and erysipelas.[45,46] The German physician Friedrich Julius Rosenbach isolated streptococci from the pus of an infected wound 2 years later and named it *S pyogenes* (from Greek *pyon* for pus, and *genein* which means to produce).[47] He believed the streptococci from pus were separate from erysipelas-associated streptococci. This controversy was only resolved with improved identification techniques,[48] and the publication of the streptococcal classification system by Rebecca Lancefield in 1933. This classification system was based on the carbohydrate composition of bacterial cell-wall antigens, and *S pyogenes* was classified as group A.[49]

The 19th century ended with miasma theory being superseded by germ theory and an improved understanding of gangrene associated with penetrating wounds. With this shift in understanding, the management of infectious diseases advanced. Although limiting the spread to others through infection control had been the focus of Middleton's trial of bromine,[10] a microbiological rationale for these measures now existed. However, infection eradication did not become the focus of hospital gangrene management until the 20th century, through surgical advances and antibiotic discovery.

Early 20th century: the surgeon's scalpel and the antibiotic chemists

> "Prior to the war, the surgeon gave most of his attention to aseptic methods, his great object being to exclude microbes from the wound. The question of how to deal with the bacteria after they were in possession was a problem of much less interest to him."[35]

Although the term necrotising fasciitis was not coined until after World War 2, several clinical syndromes resembling necrotising fasciitis were described in the early 20th century in association with traumatic processes including childbirth, burns, and penetrating war wounds

CONDENSED TABULAR STATEMENT OF CASES OF HOSPITAL GANGRENE.

	Whole Number.	Recovered.	Died.	Amputations.	Average duration of treatment.	Percentage of deaths.
Treated with Bromine, in any way, - - -	152	148	4	0	5 days and 14 hours.	
Treated with Bromine, pure, exclusively, - -	27	25	2	0	2 do. " 23½ do.	
Treated with Bromine, in solution, exclusively, -	86	84	2	0	6 do. " 11½ do.	2.65
Treated with Bromine, pure, after the solution failed,	8	8	0	0	12 do. " 18 do.	
Treated with Bromine, after Nitric Acid had failed,	23	22	0	1	3 do. " 16½ do.	
Treated with Bromine after other remedies failed, -	8	8	0	0	3 do. " 4 do.	
Treated with Nitric Acid exclusively, - - -	13	5	8	0	3 do. " 14½ do.	61.54
Treated with other remedies exclusively, - - .	13	7	5	1	7 do. " 13½ do,	38.47 } 50
Treated with other remedies after Bromine had failed,	4	4	0	0		

Figure 2: **Results of the trial of bromine for the treatment of hospital gangrene undertaken by Middleton Goldsmith in Louisville, KY, USA during the American Civil War**
Reproduced with permission from *A report on hospital gangrene, erysipelas and pyaemia: as observed in the Departments of the Ohio and the Cumberland with cases appended.*[10]

	Location	Presentation (N) and cause	Management
Penetrating wounds caused by explosives[12,35]	Boulogne, France	Infected wounds (210) from penetrating trauma; 177 (84%) of 210 isolated streptococci	Avoid antiseptics, irrigate wounds with hypertonic saline, and debridement of dead infected tissue
Haemolytic streptococcal gangrene[2,13]	Peking Union Medical College, Peking, China	Haemolytic streptococcal gangrene (20); seven (41%) of 17 blood cultures positive for haemolytic streptococcus	Surgical debridement, hygiene and infection control measures, and wounds irrigated using Dakin's solution
Puerperal sepsis[50,51]	Queen Charlotte's Hospital, London, UK	Haemolytic streptococcal puerperal fever (38 and 26 cases); 36 (95%) of 38 and 25 (96%) of 26 group A streptococcus	Treatment with sulphonamides (prontosil), and effective infection control
Infected open wounds during World War 2[52–54]	France	Haemolytic streptococcus isolated from wound infections	Dusting of wounds with sterile sulphonamide powder (American soldiers in a first aid kit) or given systemically
Patients with burns[55]	Glasgow Royal Infirmary, Glasgow, UK	Infection contaminating burns (516); 69 (13%) of 516 haemolytic streptococcus	Treatment in specialised burn units, cubicle isolation to minimise contamination, strict barrier nursing, and chloroxylenol disinfectant

Table 1: **Patterns of injury or trauma leading to *Streptococcus pyogenes* gangrene and recommended management of these cases during the early 20th century**

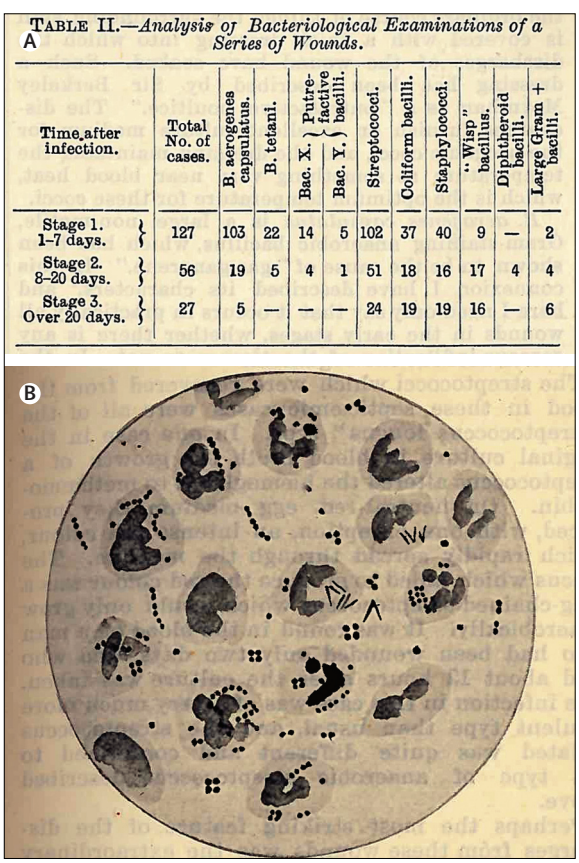

TABLE II.—*Analysis of Bacteriological Examinations of a Series of Wounds.*

A

Time after infection.	Total No. of cases.	B. aerogenes capsulatus.	B. tetani.	Putrefactive bacilli. Bac. X.	Putrefactive bacilli. Bac. Y.	Streptococci.	Coliform bacilli.	Staphylococci.	"Wisp" bacillus.	Diphtheroid bacilli.	Large Gram + bacilli.
Stage 1. 1–7 days.	127	103	22	14	5	102	37	40	9	—	2
Stage 2. 8–20 days.	56	19	5	4	1	51	18	16	17	4	4
Stage 3. Over 20 days.	27	5	—	—	—	24	19	19	16	—	6

B

Figure 3: **Analysis of bacteriological examination of a series of wounds undertaken by Alexander Fleming of the Royal Army Medical Corps while stationed in Boulogne, France during World War 1**
(A) The different bacteria seen in wounds during three different stages, based on the days after infection. Streptococci are present in all stages of infection. (B) Drawing from films of pus taken from wounds showing the late stage of infection with pyogenic cocci, wisp bacilli, and many pus cells. Reproduced with permission from *On the bacteriology of septic wounds.*[12]

(table 1). Barrier nursing and infection control, antimicrobial treatment, and effective debridement of necrotic tissue are consistent themes in the medical literature from this period (table 1). Although infection control was rooted in the hospital gangrene pioneers of the 19th century, much of the modern management of necrotising fasciitis is based on work done during the World Wars.

Streptococci and wounds during World War 1

The Scottish physician-scientist Alexander Fleming described the predominance of streptococci in war wounds in 1915.[12] While stationed in France with the Royal Army Medical Corps, he studied the bacterial flora of over 200 wounds and described a transition between early stage infections, which contained anaerobic organisms, to late-stage infections containing mainly pyogenic cocci (figure 3). Penetrating traumatic wounds contained streptococci and he implicated short-chained streptococci in the development of gangrene. Additionally, blood cultures from febrile wounded soldiers isolated streptococci. Fleming thus noted, "streptococcus is without doubt the most important member of this group as regards infection of wounds."[12] His management was not to rely on antiseptics alone because they did not penetrate into deep tissues. He encouraged irrigation with hypertonic saline[35] and emphasised surgical debridement: "...if it were possible for the surgeon to remove completely the dead tissue I am quite sure the infections would sink into insignificance".[12]

During World War 1, surgical techniques were refined to manage infected wounds. The pioneering French military vascular surgeon Alexis Carrel and biochemist Henry Dakin devised a wound-care technique using a chlorine-based disinfectant (Dakin's solution) and rubber Carrel tubes for wound irrigation.[56] Belgian surgeon Antoine Depage proposed that Dakin's solution be introduced after tissue debridement, excision of contaminated tissue, and epluchage ("peeling" of wounds before dressing).[57] Depage advocated delayed primary wound closure depending on the bacteriology and noted that "for streptococci infection never to suture but to submit the wound to adequate treatment...to wait until the

streptococci had disappeared, or had become attenuated sufficiently to permit primary union".[57] He has been credited with making the most important contribution to wartime surgery during any war.[58]

Between the World Wars and the start of the antibiotic era

In 1924, Frank Meleney, an American missionary surgeon working in China, reported an outbreak of 20 cases of haemolytic streptococcal gangrene in a Peking hospital, with 20% mortality. Meleney showed that surgery is needed to reduce mortality,[2,13] and noted that gangrene was caused by either anaerobic bacteria or haemolytic streptococci. He noted that the "infection usually starts from a superficial break in the skin, a scratch, a hypodermic injection, a cut, a pimple, or a boil but occasionally develops without any point of origin", implying that penetrating trauma is not a prerequisite for necrotising fasciitis. Meleney successfully treated cases of gangrene with bear-claw scratch debridement,[2,13] building on the work of World War 1 surgeons. In this method, single, long incisions were made to the deep fascia on either side of the affected limb (similar to the appearance of a scratch from a bear claw) to just beyond the necrotic area. Extending incisions too far spread infection, but if done correctly, this method negated the need for amputation.[13] The bear-claw technique was subsequently superseded in favour of more extensive fascial exposure and debridement.[59]

In 1932, the German histopathologist and bacteriologist Gerhard Domagk reported that mice and rabbits given the red dye prontosil rubrum, derived from sulphanilamide, survived lethal infections with haemolytic streptococci and staphylococci.[60] He received the Nobel Prize for Medicine in 1939 for his work on the sulphonamides, which revolutionised the treatment of infected war wounds. Studies in animals showed the benefit of sulphonamides in preventing wound infections when sprinkled in the wound.[51] During World War 1, 8·3% of wounded soldiers in the US army died. Mortality was reduced to 4·5% in World War 2, during which American soldiers were issued sulphonamide powder in first-aid packs. Furthermore, improved surgical techniques probably contributed to the fall in deaths of soldiers.[52,61] The use of sulphonamide on wounds escalated from 1942, but rather than sprinkling, the drug was dumped in lumps on wounds, thereby reducing drug absorption. Meanwhile, the importance of adequate wound debridement was neglected. Wounds became infected, and thus it was misinterpreted that sulphonamide powder was detrimental to wounds.[58] Leonard Colebrook, a contemporary of Fleming, also investigated the use of sulphonamides to treat puerperal sepsis,[50,62] which is usually attributed to GAS and follows maternal tissue injury during childbirth.[63] Colebrook successfully treated 38 patients with haemolytic streptococcal puerperal fever with sulphonamides, reducing mortality from 24·4% in 1935 to 4·7% in 1936.[50,64]

After World War 1, Fleming returned to work at St Marys' Hospital in London. In 1929, he described the antibacterial properties of penicillin, which was produced from the mould *Penicillium rubrum*.[35] However, it was not until 1939 that biochemist Ernst Chain and pathologist Howard Florey, along with colleagues Edward Abraham and Norman Heatley, working at the Dunn School of Pathology in Oxford, UK, were able to produce sufficient penicillin to do clinical trials.[14] Florey, Chain, and Fleming were awarded the 1945 Nobel Prize for Medicine for their discovery.[65]

Insufficient funds for research led Florey and Heatley to the USA in June 1941 to gain the support of the American pharmaceutical industry. Through improved deep fermentation techniques and isolation of *Penicillium* strains with higher penicillin yields, further clinical trials in military and civilian populations took place and sufficient penicillin was produced to accompany troops for the D-Day landings.[66] Penicillin use during World War 2 was clearly documented.[67,68] British Army surgeons in Italy prevented wound infections by inoculating penicillin-sulphathiazole powder into wounds following debridement in field hospitals; however, there was "…no tendency on the part of surgeons to neglect surgery and rely too much on penicillin".[67,68] Clearly, for traumatic battle wounds, surgery was the main priority, although a combination of surgery and penicillin was emphasised, "…for the knife alone cannot get rid of infection".[67,68]

Infection control revisited: World War 2 and the mid-20th century

In 1847, Ignaz Semmelweiss showed the importance of handwashing for the prevention of puerperal sepsis.[69] During World War 2, nosocomial transmission of GAS was a recognised problem.[6] Thus, the role of infection control was revisited. Wards were reorganised to prevent patient-to-patient transmission, and environmental sampling and cleaning were introduced. Health-care workers were advised to clean hands and use masks and sterile instruments. A wound-dressing technique was developed that included so-called clean and dirty nurses.[6,70] The dirty nurse and a dresser would remove and apply bandages to a patient's wound, washing their hands between patients. Meanwhile, the clean nurse would not have direct patient contact and would look after the contents of the dressing trolley only, washing their hands only after the dressing round. This method reduced GAS wound infection from 15·4% to 1·1% in one wartime neurosurgical unit.[70] Many practices advocated during this time are still recommended for the prevention of nosocomial transmission of GAS nowadays.[71]

In 1952, Ben Wilson, a surgeon at Parkland Hospital, Dallas, TX, USA, coined the term necrotising fasciitis, which was adopted into widespread use. He reported that fascial necrosis was a consistent manifestation in

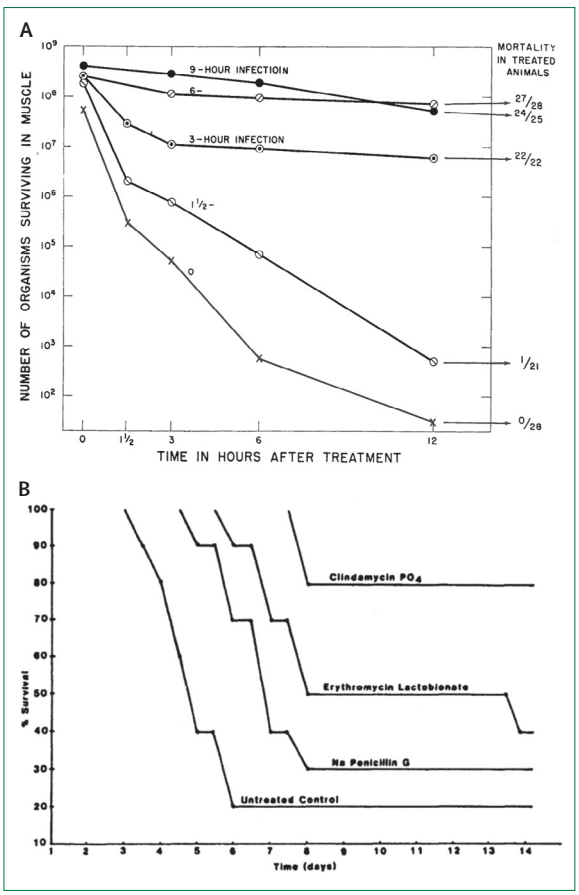

Figure 4: **The Eagle effect in an in vivo model of myositis**
(A) Eagle showed in vivo the reduced bactericidal effect of delaying penicillin treatment. Mice were infected intramuscularly with 5×10^7 *Streptococcus pyogenes*, divided into groups (0, 1·5, 3, 6, and 9 h), and given procaine penicillin (0·15 cc of suspension at 10 000 units/mL). Each point represents the median number of organisms recovered from the infected muscle tissue. The mortality of the animals increased as treatment was delayed. Eagle suggested that the reduced activity of penicillin in older infections is not only caused by the large number of organisms, but also caused by the likely physiological state of the bacteria and the host tissue environment. Reproduced with permission from Experimental approach to the problem of treatment failure with penicillin. *I. Group A streptococcal infection in mice.*[74]
(B) The Eagle effect was later revisited by comparing penicillin, erythromycin, and clindamycin in mice with myositis. When treatment was delayed to 6 h postinfection, mice given penicillin had a similar mortality to untreated control animals, whereas 80% of the clindamycin group survived. Reproduced with permission from The Eagle effect revisited: efficacy of clindamycin, erythromycin, and penicillin in the treatment of streptococcal myositis.[75]

22 patients admitted at the hospital from 1948 to 1951, and in previous cases reported in the medical literature.[3] He also noted that necrotising fasciitis "…may start in an operative wound, in a trivial injury…or may appear spontaneously".[3] Notably, although haemolytic streptococci were cultured from all of Meleney's cases,[13] haemolytic bacteria were grown in pure culture in 58% of Wilson's cases studied bacteriologically, of which 88% were identified as staphylococci.[3] Furthermore, mortality in Wilson's cohort was only 8·7% compared with 20% reported by Meleney. Wilson stressed the importance of early recognition, prompt surgery, penicillin, and support for abnormal physiology.[3]

By the mid-20th century, infection control advocated by American Civil War surgeons was combined with antibiotics targeted at *S pyogenes* and effective surgical debridement, as emphasised by Fleming, Meleney, and Wilson, in the battle against streptococcal gangrene. Indeed, after World War 2, reports of GAS necrotising fasciitis in conflicts in Korea, Vietnam, and the Falklands were rare, perhaps because of the measures described, which resulted in fewer infections. However, the effectiveness of penicillin was questioned, and the last two decades of the 20th century saw a worldwide re-emergence of invasive GAS infections.

Late 20th century: the Eagle effect, immunoglobulins, and hyperbaric oxygen

The development of penicillin was a major transition point in the management of necrotising fasciitis. However, in 1948, Harry Eagle described the Eagle effect, the paradoxical reduced antibacterial effect of penicillin against various *Staphylococcus* and *Streptococcus* species when given at high doses in vitro.[72] GAS were not subject to the Eagle effect, and no GAS isolates have been resistant to penicillin.[73] However, treatment failure despite penicillin sensitivity and high mortality associated with severe disease led to the hypothesis that when GAS reaches the stationary growth phase—eg, where the initial infection is with a large number of bacteria—expression of penicillin-binding proteins is reduced and susceptibility to β-lactams is diminished.[21,74] Eagle also showed that delayed initiation of treatment with penicillin after infection with GAS in a mouse model of myositis resulted in an apparent reduction in bactericidal effect (figure 4).[74] In the 1980s, this effect was revisited. The efficacy of penicillin, erythromycin, and clindamycin were compared in mouse models of GAS myositis and, unlike penicillin, the efficacy of clindamycin was not adversely affected by a heavy burden of infection (figure 4).[75] This finding lent support to the use of clindamycin for necrotising fasciitis treatment (in combination with a penicillin), particularly when necrotising fasciitis was associated with toxic shock syndrome, because clindamycin inhibits toxin production.[76] Retrospective clinical studies have generally been supportive of adjunctive clindamycin therapy in severe disease;[77–79] however, outbreaks by clindamycin-resistant GAS[80] could limit the usefulness of this drug.

STSS and GAS septic shock have a high mortality and are associated with almost 50% of necrotising fasciitis cases.[18] Patients need supportive measures in a high dependency or intensive care setting. Additionally, intravenous pooled human immunoglobulin has been advocated. Bacterial toxins, including superantigens, lead to the release of inflammatory cytokines, tissue destruction, and shock.[81] Augmenting the humoral immune response with intravenous immunoglobulin neutralises superantigens,[82] enhances GAS clearance,

and has an anti-inflammatory effect.[83] Owing to the rise of variant Creutzfeldt-Jakob disease in the 1990s,[84] the use of intravenous immunoglobulin is strictly controlled in the UK and elsewhere. Studies assessing intravenous immunoglobulin in severe invasive GAS disease are scarce. One randomised, double-blind, placebo-controlled trial[85] was underpowered to reach statistical significance because of the small numbers of patients recruited.[85] Retrospective reports are complicated by many confounding factors, including use of historical controls with higher mortality rates[86] or children with less severe disease.[87] In 2014, two retrospective cohort analyses seemed to favour intravenous immunoglobulin in severe invasive GAS, but both studies had small numbers of patients and were again underpowered.[77,88] The large sample size needed for clarification of the role of intravenous immunoglobulin in this rare disease[89] means that the definitive answer is not forthcoming.

Hyperbaric oxygen therapy was another approach to treatment studied in the late 20th century. This adjunctive therapy is thought to increase tissue partial pressure of oxygen up to four times normal, thus increasing bacterial killing and facilitating wound healing.[90] However, the few studies that have investigated hyperbaric oxygen therapy in GAS necrotising fasciitis show little outcome benefit,[91–93] and transferring patients to a centre with hyperbaric oxygen therapy might delay effective surgical debridement.[91,94]

Diagnosis is still one of the most challenging aspects of management of GAS necrotising fasciitis. Diagnostic delay is common in historical and current medical literature[2,33] and could result in adverse outcomes.[33] The innocuous appearance of the infection, relation to muscle contusion, or attribution of pain to an injury might delay presentation or mislead clinicians.[31,33] Skin discolouration, blistering, and visible necrosis are late features of necrotising fasciitis and are ominous signs. Nowadays, imaging and frozen sections with good histological examination might help diagnosis, but intraoperative assessment and exploration is preferable when diagnostic uncertainty is present.[95]

Worldwide GAS resurgence and the association with trauma

Since the 1980s, GAS diseases, such as necrotising fasciitis and STSS, have resurged worldwide.[96] GAS infects wounds in which skin integrity has been broken;[97] however, blunt trauma leading to muscle contusion preceding GAS necrotising fasciitis is also recognised (table 2).[27–33,98,99,102] In larger studies of GAS necrotising fasciitis from North America and the UK, non-penetrating trauma or injury was present in about 25% of cases of necrotising fasciitis.[18,103–105] In a case-control analysis, a significant association was noted between non-penetrating trauma and GAS necrotising fasciitis, but not cellulitis.[106] Other predisposing factors include burns, surgery, and varicella infection. Varicella infections are often problematic because of secondary bacterial infections, including necrotising fasciitis,[107,108] and in countries where children receive the varicella vaccine, paediatric invasive GAS has become less common.[109]

GAS necrotising fasciitis generally affects more men than women, although this difference might result from reporting bias. Furthermore, many cases of GAS necrotising fasciitis have no obvious portal of entry. For example, in a cluster of six necrotising fasciitis cases in the UK, two had no predisposing history;[110] eight of 20 patients with invasive GAS infection in the USA had no portal of entry;[20] and five of 14 consecutive necrotising fasciitis cases over 5 years in northern Australia had a similar lack of relevant history.[91] Occasionally, patients reported mild upper respiratory tract infection.[111] Diabetes, obesity, and chronic alcohol use also predispose an individual to necrotising fasciitis.[23,112,113]

The management of patients in these reports is similar: initial broad-spectrum antibiotics, rationalised to benzylpenicillin and clindamycin once GAS is identified. Surgical debridement is always done, and repeated intervention is often necessary. Mortality is high, despite intensive care support, and patients have long hospital stays and need long-term rehabilitation (table 2).

The worldwide resurgence of GAS has been documented specifically in military personnel. Training facilities have seen outbreaks of the whole spectrum of GAS disease including pyoderma, ecthyma, necrotising fasciitis, and STSS, and postinfectious sequelae including rheumatic fever and glomerulonephritis.[114–117] This morbidity among military cohorts has been attributed to crowded conditions, reduced hygiene, and an absence of type-specific immunity. Consequently, the US military has used prophylactic penicillin (or macrolides in soldiers with penicillin allergy) in basic military trainees since 1953.[118–120]

Necrotising fasciitis and gas gangrene caused by pathogens other than GAS

GAS was historically the most commonly recognised cause of necrotising fasciitis; however, widespread use of antibiotics and improved bacterial identification have increased the diversity of bacteria found in penetrating wound infections, many of which are polymicrobial and contain resistant organisms. In 2010, an earlier classification[121] was updated and necrotising fasciitis was divided into four aetiological types: polymicrobial necrotising fasciitis (type I), as distinguished from monomicrobial necrotising fasciitis caused by Gram-positive bacteria (type II), Gram-negative bacteria (type III), or fungi (type IV).[122] Some case series report necrotising fasciitis as being mostly polymicrobial,[112,123,124] whereas in others, single pathogens are more common.[125–127] However, limitations in culture methods might explain these findings.[125] Meticillin-resistant *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Vibrio parahaemlyticus*, and

	Age (years)	Sex	Country	Site	Risk factors	Cause	Trauma	Mortality	Management
Adams et al[27] (n=2)	58 and 40	1 male, 1 female	USA	Limb	None	*Streptococcus pyogenes*	Skin injury	100%	Surgical debridement, intravenous penicillin, and ITU support
Svensson et al[98] (n=4)	38, 29, 43, and 41	1 male, 3 female	South Africa	Arm	Obesity	75% isolated *S pyogenes*	Contusion of arm	50% of *S pyogenes* cases	Debridement and intravenous penicillin, tobramycin, and metronidazole
Hird et al[30] (n=1)	17	Male	USA	Thigh	None	*S pyogenes*	Bruise from sport	100%	High-dose benzylpenicillin, fasciotomy and debridement of thigh, and ITU support
Sellers et al[99] (n=8)	Mean 46 (range 32–63)	6 male, 2 female	USA	6 limb, 2 GAS pneumonia with pupura fulminans	5 of 8 had a history of chronic illness (alcohol abuse, cirrhosis, COPD, or previous GAS cellulitis)	*S pyogenes*	2 blunt trauma, 1 bee sting, and 1 ulcer	25%	Surgical debridement, and 6 of 8 patients started on clindamycin in combination with penicillin or cephalosporins. 1 given clindamycin, vancomycin, and imipenem and cilastin. 1 given vancomycin and ceftriaxone
Nothwang et al[28] (n=1)	19	Male	Germany	Thigh	None	*S pyogenes*	Fall on side	0%	Debridement and ITU support; antibiotic regimen not described except for candida sepsis with diflucan
Hirose et al[100] (n=1)	36	Female	Japan	Right hip	None	*S pyogenes*	Injury to right hip	100%	Supportive care as arrived at hospital in extremis
Dahl et al[101] (n=2)	61 and 32	Both male	USA	Hand	Rheumatoid arthritis (61 years old)	*S pyogenes*	Blunt trauma to the hand	50%	Debridement, ITU support, clindamycin, penicillin, and intravenous immunoglobulin
Jallali et al[29] (n=1)	42	Male	UK	Anterior chest wall	Epilepsy and heavy alcohol intake	*S pyogenes*	Collapse following convulsion	0%	Ceftriaxone, flucloxacillin, and metronidazole changed to benzylpenicillin, ciprofloxacin, and clindamycin owing to intraoperative findings, surgery, and ITU support
Raffoul et al[32] (n=1)	46	Female	France	Hand and arm	None	*S pyogenes*	Contusion	0%	Surgery and antibiotics not specified
Heinze et al[31] (n=1)	47	Male	Germany	Leg	Likely NSAID injection	*S pyogenes*	Minor trauma to left leg during tennis	100%	Surgical exploration and debridement; antibiotic treatment not mentioned
Radovan et al[102] (n=2)	48 and 57	1 male, 1 female	Serbia	Chest wall, upper limb, and trunk	NSAIDs (naproxen, aspirin, and diclofenac)	*S pyogenes*	Injury, and fall	100%	Died on admission
Baker[33] (n=1)	33	Male	UK	Hamstring	None	*S pyogenes*	Muscle strain	100%	Surgical exploration and amputation; no antibiotics

ITU=intensive treatment unit. GAS=group A streptococcus. COPD=chronic obstructive pulmonary disease. NSAID=non-steroidal anti-inflammatory drug.

Table 2: **Case reports showing the potential association between blunt trauma or non-penetrating muscular injury and the development of *Streptococcus pyogenes* necrotising fasciitis**

Actineobacter baumanii have all been isolated, with the predominant organism dependent on geography.[36,125–129]

One form of polymicrobial necrotising fasciitis is Fournier's gangrene, a necrotising perineal and genital infection first described in healthy young men by venereologist Jean-Alfred Fournier in 1883. He also noted the association of gangrene with diabetes, alcoholism, and urological trauma.[130] Organisms in Fournier's gangrene are usually commensals, with aerobic and anaerobic bacteria acting synergistically through mutually beneficial nutrient and toxin production.[131] Widespread antibiotic use has resulted in bacterial resistance, necessitating the use of broad-spectrum antibiotics for this disorder at the outset.[132]

No historical review of necrotising fasciitis would be complete without mentioning the ubiquitous Gram-positive anaerobic bacterium, the *Clostridium* spp. Gas gangrene, also known as clostridial myonecrosis, has been associated with soil containing *Clostridium* spp, which contaminates battlefield wounds. Estimates of the incidence of gas gangrene in the wounded during World War 1 are about 10%, and less than 1% for World War 2.[133] Although advances in weaponry led to tissue destruction favouring anaerobic growth, improved surgical techniques including debridement and delayed primary closure reduced mortality from gas gangrene.[134] *Clostridium perfringens* was historically the most common cause of necrotising infections resulting from penetrating trauma; however, *Clostridium septicum* and *Clostridium sordellii* have also been implicated in infection at sites of minor injury.[135]

Into the 21st century: molecular pathogenesis of GAS necrotising fasciitis

The development of molecular biology over the past 40 years has improved our understanding of the mechanisms by which GAS causes disease. GAS affects only human beings and usually colonises people via the nasopharynx or skin. After colonisation, immune evasion is a prerequisite for bacterial invasion and establishment of deep tissue infection. Molecular biology has improved our understanding of the pathogenesis of GAS necrotising fasciitis (figure 5).

GAS expresses several virulence factors to evade humoral immune effectors.[137,140–142,145] The best studied GAS virulence determinant is the M protein. Although there are more than 100 M serotypes, M1 and M3 isolates predominate in invasive disease.[146,147] This predominance is probably related to virulence genes carried by these M types, coupled with a serotype-specific ability to evade the immune response. Through its interaction with host immune proteins, the M protein itself might help invading bacteria. Additionally, some necrotising fasciitis pathophysiology might be attributable to M protein binding fibrinogen, which initiates a cascade resulting in vascular leakage and toxic shock.[148]

GAS has several mechanisms to evade neutrophils, key players in host innate immunity, such as the hyaluronic acid capsule, streptolysins, and DNases.[141,149,150] GAS expresses the protease SpyCEP that cleaves the chemokine interleukin 8, which is involved in the recruitment and activation of neutrophils,[143] perhaps explaining the scarcity of neutrophil infiltrates in histopathological sections from cases of severe necrotising fasciitis. SpyCEP enables survival and dissemination of GAS,[151] and high SpyCEP activity is associated with increased disease severity and poor clinical outcome.[143] Other GAS proteases are implicated in immune evasion and the pathological changes noted in necrotising fasciitis.[137,139,142] Notably, the cysteine protease SpeB might be associated with tissue necrosis[139] and phenotypic switching of bacteria during invasive infection.[138] Genetic reasons behind the aggressive phenotype of GAS isolates causing necrotising fasciitis are also being established. For example, mutations in the CovR/S regulatory system, which enables the bacteria to respond to their environment, occur readily in M1 isolates. CovR/S mutations are associated with invasive bacterial phenotypes with reduced SpeB production and increased SpyCEP expression.[143,144] Furthermore, a single-nucleotide polymorphism in the *mtsR* gene of some M3 isolates, which encode a transcriptional regulator, is associated with a reduced propensity to cause necrotising fasciitis.[152] Other virulence determinants have been implicated in necrotising fasciitis pathogenesis, and the unique mechanisms by which GAS is exquisitely adapted to its host.[153]

To replicate the finding that GAS necrotising fasciitis can occur with minor injury, mice inoculated with GAS were bruised at a site distant to the original inoculation. The investigators reported higher mortality than that in unbruised controls, implying that distant muscle sites might harbour bacteria.[154] Furthermore, M1 and M3 GAS adhere to damaged skeletal muscle cells, possibly via cytoskeletal vimentin,[155] and, in mice, GAS seed to moderately damaged muscle after non-penetrating injury (in association with upregulated vimentin expression).[156] Although these studies have their limitations, they suggest a possible mechanism for the association of GAS necrotising fasciitis and non-penetrating trauma.

Our understanding of GAS molecular pathogenesis has not had a profound effect on management of necrotising fasciitis. Ultimately, molecular biology might lead to a GAS vaccine, which would prevent the whole GAS disease spectrum. GAS vaccine development has a long and varied history, and was discussed by Fleming in 1915.[12] Inactivated whole-cell vaccines were unsuccessful in the 1940s,[157] and M protein-containing vaccines have only slowly advanced to clinical trials.[158,159] Other vaccine targets include SpyCEP[160] and C5a peptidase.[161] Because necrotising fasciitis is rare, the success of vaccines at preventing GAS necrotising fasciitis and other invasive GAS infections will be difficult to quantify and a surrogate of protection is needed.

Conclusion

Despite postoperative supportive care on technologically advanced intensive care wards, and adjunctive therapies such as intravenous immunoglobulin and hyperbaric oxygen, the outcome from GAS necrotising fasciitis

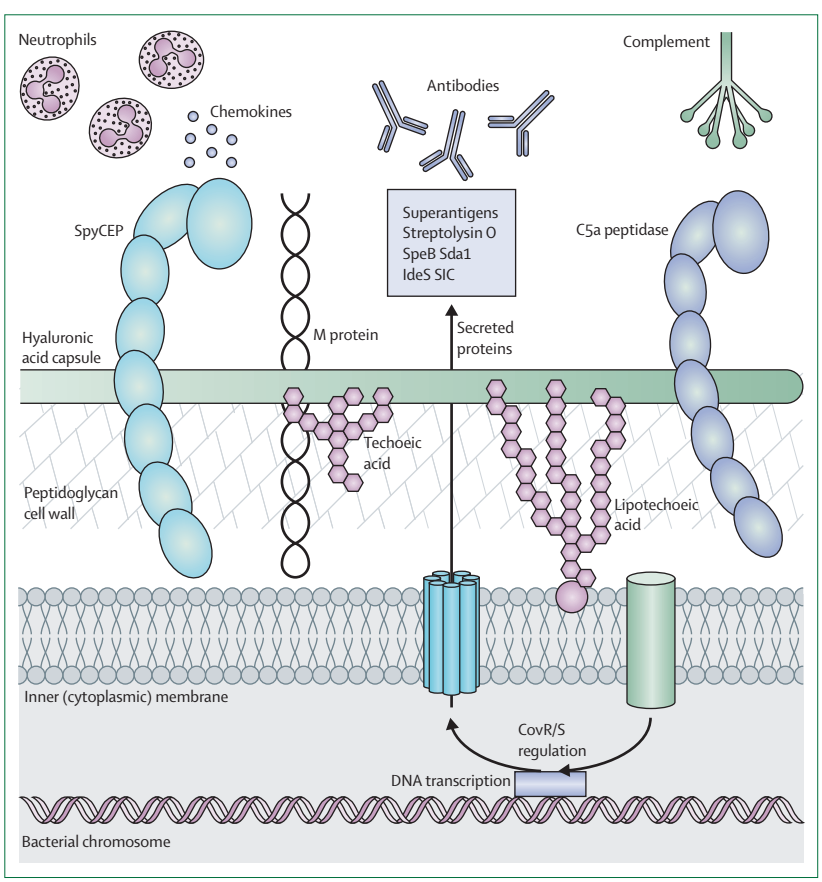

Figure 5: **Bacterial virulence factors associated with invasive streptococcal disease**
Streptococcus pyogenes possesses several virulence factors, which enable the bacteria to evade the host innate and adaptive immune defences and establish a deep tissue infection. Surface-expressed proteins such as the M protein and C5a peptidase are implicated in complement evasion,[136,137] whereas SpyCEP and C5a peptidase affect neutrophil recruitment. The secreted protein SpeB is implicated in tissue necrosis in necrotising fasciitis and phenotypic switching of bacteria in invasive infection.[138,139] Other secreted proteins include: SIC that helps complement and antimicrobial peptide evasion,[140] the DNAase Sda1 that acts on neutrophil-derived extracellular traps,[141] and the immunoglobulin-degrading protein IdeS.[142] The two component regulatory system CovR/S is implicated in the regulation of some of these virulence factors and might be associated with more invasive bacterial phenotypes.[143,144]

Search strategy and selection criteria

We searched PubMed with no date restrictions for articles published in English, French, or German using the following keywords: "necrotising fasciitis", "hospital gangrene", "group A streptococcus", "*Streptococcus pyogenes*", "Goldsmith", "bromine", "Eagle effect", "bear claw", and "trauma". We also searched Google Scholar, Imperial College, and the British Library using the same keywords. Articles resulting from those searches and relevant references cited in the articles were reviewed.

remains poor. Mortality is as high as 40%,[22] which is almost 20-times greater than that in Goldsmith's patients who were given bromine in 1863.[10] In the authors' experience, failure to recognise necrotising fasciitis contributes to the high death rate. Why the mortality remains so high is unknown. Although historical reporting bias might contribute, an alternative view is that GAS has become more virulent.[20,21] Developments in molecular biology will hopefully answer this question and lead to improved disease prevention through an effective GAS vaccine, which would be the ultimate successor to bromine, bear-claw scratch fasciotomies, and the Eagle effect.

Contributors

LEML conceived the manuscript and undertook the initial literature search. LKKT and LEML prepared the figures. All authors contributed to the writing of the report, and reviewed and approved its final version.

Declaration of interests

We declare no competing interests.

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